any efficacy data in the moderate to severe that would warrant changing to over-the-counter.

CHAIRPERSON GULYA: Thank you.

Dr. Mair?

DR. MAIR: Eric Mair. In our study looking at these popular snoring aids, I went down on the internet and Googled to find out what were the most popular snoring aids out there, what is out there on the market, number one, two, and three.

The one, two, and three that we looked at were a nasal dilator, the Strip, just one of the nasal dilators. The second thing was these cervical pillows. We did the same study that I talked about previously with the cervical pillows and found the exact same results, that there was absolutely no objective or subjective change in snoring. I realize they are already over the counter. The problem that I have, though, stems more with the mild obstructive sleep apnea.

The article that we were given in our packet to review is "Cervical Positional Effects on Snoring and Apneas." In this article, there was one,

I guess the premier article, leading to the OTC approval. We see that it looks at three patients with mild obstructive sleep apnea. And the RDI goes from 14.7 to 10.5. So they still have obstructive sleep apnea at the beginning and at the end. And there are only three patients in the study.

I am concerned that now we have a product that is over the counter for treating obstructive sleep apnea. And I am not sure if our data really shows this. I don't think that it shows it for snoring. I am even more concerned that we're telling our patients that "Well, it was cleared by FDA or is approved by the FDA for over-the-counter use."

CHAIRPERSON GULYA: Thank you very much.

Dr. Suzuki?

MEMBER SUZUKI: Jon Suzuki. I believe there is insufficient data for its use in the application for moderate to severe OSA.

CHAIRPERSON GULYA: Thank you.

Dr. Zuniga?

MEMBER ZUNIGA: No further comment.

CHAIRPERSON GULYA: Okay. Thank you.

Dr. Zero?

MEMBER ZERO: Again, I agree that there is not sufficient data to support increasing or extending the OTC classification to the other categories. I guess the next question will address whether we need to review its current status.

CHAIRPERSON GULYA: Okay. Thank you.

Dr. Woodson?

DR. WOODSON: I would agree. We probably should look at its current status. It doesn't look like there is data for either OSA or snoring. And it looks really uncomfortable, too.

CHAIRPERSON GULYA: A tennis ball would be better.

DR. WOODSON: Yes.

CHAIRPERSON GULYA: Dr. Stern?

DR. STERN: Yes. Carolyn Stern. The cervical pillows, I also note that there are some that are by prescription and some that are over the counter.

CHAIRPERSON GULYA: There's one.

DR. STERN: So that part is not even in

there, and I was just wondering about that but no other comment.

CHAIRPERSON GULYA: Eric, would you be able to address that issue? I think it was in your presentation that you had one of these pillows that was prescription still and one of them that's over the counter or was that a transition? Was it originally prescription and then it transitioned to being over the counter?

DR. MANN: Yes. The first cervical pillow that was cleared for an indication of snoring in mild sleep apnea was the PillowPositive pillow from Life Sleep Systems. It had been previously marketed as a snoring pillow, but the did come in with a 510(k) for the new mild obstructive sleep apnea indication. That was supported by clinical data, one of the articles of which was included.

And this was the initial kind of pilot study. So it was a small number of patients. There was an additional study that was published. I did not include that in there. It had more patients and substantiated the initial findings of this pilot

study. I did not put that article in there as stating the basis of our clearance of the product for that indication. It was merely to illustrate the types of studies that had been done in the past to support these kinds of indications.

So that was indeed a prescription device, that first pillow. And subsequent to that, we received two additional 510(k)'s for over-the-counter treatment of snoring and obstructive sleep apnea.

DR. ROSENTHAL: I think the question is, is it still a prescription device that can be bought over the counter or is it an over-the-counter device that can be bought over the counter without a prescription?

DR. MANN: The sponsor has not come back in with a 510(k) seeking over-the-counter status.

DR. ROSENTHAL: So it's a prescription device that is sold over the counter, which means it has to be prescribed by a medical professional. And then they can go in and just buy it.

DR. MANN: I'm not aware that it's being sold over the counter.

DR. ROSENTHAL: Am I wrong?

DR. MANN: PillowPositive?

DR. LI: Kasey Li. I was actually involved with PillowPositive. The material of the material for the prescription is different than what is available over the counter. My understanding was that the company no longer exists.

I don't know what the status of that is, but I think there is a major issue in terms of extrapolating the data from the PillowPositive from all of the other "snoring pillow" because they are very different.

And the same goes along with all of these different products that we're basing specific data on specific product and trying to extrapolate with others. Often they don't apply.

DR. MANN: That's an issue that really kind of confronts us when we receive 510(k)'s. We are presented with a clinical study to evaluate. And we basically can't do a literature search to support our decisions. We have to base our decisions on what has been submitted. I would just --

DR. LI: Specifically about the PillowPositive, it requires a custom measurement and fabrication and design of the pillow for the individual patient. Actually, they have had jigs that measure the neck and head position and shoulder position. So I am sure that is not with the other products that have been submitted since.

DR. MANN: That's correct. The other two that have received over-the-counter clearance have been pretty much a one size fits all kind of pillow. So there are no fitting issues involved.

And, as I stated before in the earlier presentation, there were a number of factors that went into the decision for the over-the-counter status: number one, some of the data, not all of which has been provided to you, supporting the effectiveness; number two, review of the labeling, which, again, clearly delineates the precautions and warnings that we have talked about in the past as well and, again, a long history of experience with the snoring pillows, no reported complications and having a safety profile very different from the oral appliances and air

devices that were discussed this morning.

So a lot of factors were taken together that played into that risk-benefit assessment for the over-the-counter.

CHAIRPERSON GULYA: Dr. Mair?

DR. MAIR: A question for you, Eric. The study that we have right here shows that the mild obstructive sleep apnea before the pillow were mild obstructive sleep apnea. After the pillow, they were mild obstructive sleep apnea. So they still have obstructive sleep apnea, and it's still mild. Do the other studies refute this?

DR. MANN: The other studies essentially were with a larger population of patients. It essentially also showed approximately a 25 to 30 percent reduction in RDI. I guess Dr. Li can probably comment on that as well.

DR. MAIR: And then the second thing is there are some published reports. So I guess our study looked at that, went over the objective complications. And they looked at morning headache was quite significant and, most importantly, was

morning neck stiffness. So they're not without problems, although they are minor compared to the positional devices.

DR. MANN: Right. And I would at some point maybe this afternoon want to revisit the issue of basically we have 40 to 60 percent of the population, adult American population, with snoring.

We have heard a lot of discussion today that signs and symptoms do not correlate well with polysomnography. There is no mix of factors in a modeling sense that can be used to predict who has snoring versus OSA. Currently we only have polysomnography, although there may be other technologies in the pipeline.

So I would like to hear from the panel, do they feel that every patient was snoring, 40 to 60 percent of the adult population needs to go for a sleep study?

CHAIRPERSON GULYA: Thank you, Dr. Mann.

Dr. Terris, would you like --

DR. TERRIS: I will address that issue this afternoon.

CHAIRPERSON GULYA: Great.

DR. TERRIS: But let me just briefly say this is totally inconsistent to have sleep apnea as an indication for one of the products and not for the others. To me, it makes zero sense whatsoever.

And because our predecessors made an error, I don't think we should propagate that error. We should fix it. I mean, that is our responsibility, to protect the public. So here is an opportunity to remove mild sleep apnea as an indication for the cervical pillows, Dr. Jenkins.

CHAIRPERSON GULYA: Dr. Rosenthal, please?

DR. ROSENTHAL: Dr. Terris, I think you don't realize that companies submit different information --

CHAIRPERSON GULYA: That's right.

DR. ROSENTHAL: -- when they submit their applications. And so we have to go on the information they submit depending on the indication which they request.

CHAIRPERSON GULYA: We have still the mandibular support devices. Dr. Mair, if it is a

burning issue, I will take your comment, but I would like to make sure we get through the issues.

DR. MAIR: A very quick comment.

CHAIRPERSON GULYA: Okay.

DR. MAIR: Eric Mair. Potentially over lunchtime, we could get that article that Dr. Mann talked about, and the panel can review that to see. I think that would be very helpful because this article that we have right now says that OTC should not be given to the pillow.

CHAIRPERSON GULYA: Yes. Okay. Ms. Howe?

MS. HOWE: Betsy Howe. I don't have any further comment on this category, but I sure look forward to the discussion on labeling.

CHAIRPERSON GULYA: Thank you. So do I.

Dr. Calhoun?

DR. CALHOUN: I do not support extending the labeling indications.

CHAIRPERSON GULYA: Thank you.

Ms. Schechter?

MR. SCHECHTER: No further comment.

CHAIRPERSON GULYA: Thank you.

DR. DEMKO: I don't think there is enough data.

CHAIRPERSON GULYA: Thank you, Dr. Demko.

Okay. Mr. Crompton?

MR. CROMPTON: And I would just like to thank Dr. Rosenthal and Dr. Mann to point out that when FDA makes a decision, it is typically not based on this packet. It's made on the 510(k) that is submitted by the sponsor. Frankly, I don't think this is the time to review clear devices.

I would point out that, again, I think the definitions now are catching up and sponsors can come forth with studies to prove the safety and effectiveness of these devices.

CHAIRPERSON GULYA: Okay. Now, I know we are getting at the lunchtime. I would really like to try and get through these mandibular support devices. Actually, what we have to do is address the risk-benefit for OTC use for snoring/mild sleep apnea.

I think if we remain focused, we can finish this and make a stampede for lunch. Is that okay with everybody? Okay. Where will I start now?

I think I will start with Dr. Suzuki.

MEMBER SUZUKI: Mandibular support devices, insufficient data.

CHAIRPERSON GULYA: Thank you very much.

Dr. Zuniga?

MEMBER ZUNIGA: I think there is insufficient data. No further comment.

CHAIRPERSON GULYA: Thank you very much.

Dr. Jenkins, you are hiding back there.

MEMBER JENKINS: I would agree.

CHAIRPERSON GULYA: Thank you.

Dr. Mair?

DR. MAIR: Insufficient data.

CHAIRPERSON GULYA: Thank you very much.

Dr. Li?

DR. LI: I agree.

CHAIRPERSON GULYA: Wonderful.

DR. ORLOFF: Same.

CHAIRPERSON GULYA: Yes. Everybody is getting weak with hunger. The fight has taken over.

(Laughter.)

CHAIRPERSON GULYA: Dr. Zero?

MEMBER ZERO: Agree.

CHAIRPERSON GULYA: Thank you very much.

Dr. Woodson?

DR. WOODSON: Agree.

CHAIRPERSON GULYA: Thank you very much.

Dr. Stern?

DR. STERN: Same.

CHAIRPERSON GULYA: Thank you.

Dr. Terris?

DR. TERRIS: I agree.

CHAIRPERSON GULYA: Wonderful.

All right. Ms. Howe?

MS. HOWE: No comment.

CHAIRPERSON GULYA: Thank you.

Dr. Calhoun?

DR. CALHOUN: I agree. And, furthermore, I think there is some potential risk when someone develops nasal obstruction during the course of the night and they can't open their mouths to breathe through them.

CHAIRPERSON GULYA: Thank you very much.

Mr. Schechter?

MR. SCHECHTER: Let's go eat.

CHAIRPERSON GULYA: Thank you.

Dr. Demko?

DR. DEMKO: I agree.

CHAIRPERSON GULYA: All right. Thank you.

Mr. Crompton?

MR. CROMPTON: No comment.

CHAIRPERSON GULYA: Okay. Great. Thank you very much.

All right. Now, we have some announcements from Sally Thornton. And then we will break for lunch.

EXECUTIVE SECRETARY S. THORNTON: This is an announcement that is lunch-related. So listen up.

CHAIRPERSON GULYA: You got our attention.

EXECUTIVE SECRETARY S. THORNTON: They're waiting lunch for us in the restaurant here, the Brasserie. And there is a special room that we have set aside for the FDA panels, Dental and ENT, to retire to have lunch together. So off you go.

DR. TERRIS: Can I request a seat next to Dr. Jenkins?

(Laughter.)

CHAIRPERSON GULYA: Okay. Now, we will resume here at 1:30 sharp. Thank you.

(Whereupon, at 12:38 p.m., the foregoing matter was recessed for lunch, to reconvene at 1:30 p.m. the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:40 p.m.)

CHAIRPERSON GULYA: I would like to call this joint panel meeting back into session. So as I see it now, we have successfully negotiated question 1. What we have now to do is to go through questions 2 and 3. We are now going from 1:30 until 3:30, at which point in time we will have another open panel hearing session here.

So question 2, to refresh everybody's memory, is if we believe that certain devices would be appropriate for OTC treatment of obstructive sleep apnea, please discuss adequate product labeling to assist a self-diagnosis and differentiation of OSA and any other general or specific labeling restrictions that you think would be appropriate.

This is a little bit of a quandary because many of the devices we believe would be not appropriate for OTC use, but if something were to change in the future, perhaps that some of these conditions might be more readily self-diagnosed, we might want to sort of lay some preparatory groundwork.

There was some difference of opinion about the appropriateness of OTC use for some of these devices.

So, again, looking at things, we probably have about an hour for question number 2 and an hour for question number 3. I think if we go through it again device by device, with individuals who are proponents for favoring over-the-counter use by each device, giving what they believe would be appropriate language, I think we can at least discuss the issue. And the FDA can take back the relevant points from our discussion and work with those in their further formulation of labeling and decisions for OTC use, where it says "prescription use."

So let's turn and look at this tongue retaining device. I know we had a pretty considerable majority not really happy about the idea of approving it for OTC use. Those individuals who would consider it for OTC use for either snoring or for one of the variety of forms of obstructive sleep apnea, do any of you have any verbiage you would suggest for how one could label this product to help the user self-diagnose to assure appropriate use and any other

labeling restrictions?

Rather than calling on people, I think we have gotten comfortable enough in jumping in that I think we can let people volunteer, although if I see too little participation, I will not hesitate to start prompting participation. Okay?

MEMBER SUZUKI: Madam Chairman?

CHAIRPERSON GULYA: Okay. Dr. Suzuki?

MEMBER SUZUKI: Jon Suzuki, Dental Products. In light of our discussions this morning, I think it is a relatively moot point to even discuss this next question. So I think it should go by the wayside.

DR. ORLOFF: Well, except that I don't think it's moot for anything that is used for snoring to have on the labeling that individuals should recognize that snoring may be a sign of sleep apnea. I don't know if that is a requirement of everything that is already approved for over the counter, but it should be if it is not.

CHAIRPERSON GULYA: Okay.

DR. MAIR: Could I ask a question, please?

CHAIRPERSON GULYA: A second question, yes.

DR. MAIR: A second question? All right. We're talking about labeling. Labeling is different for Class II than it would be for potentially over the counter. Labeling would be contradictions, warnings, precautions, what are adequate directions for fitting, for usage, and for care afterwards.

Are these the types of things that we want to discuss? Is it for a Class II-type device or how is that different from an over-the-counter?

CHAIRPERSON GULYA: Well, I think -- and, Eric, you can correct me if I am wrong here -- if we discuss both, it would probably be helpful to them. As I said, I thought there was a minority who favored potential OTC application of the tongue retaining device. And if so, then it might be appropriate to have instructions appropriate for OTC use.

Dr. Runner?

DR. RUNNER: Actually, instructions can be appropriate for any class of device in terms of what kind of labels you might consider.

CHAIRPERSON GULYA: So basically it just has to be sixth or seventh grade reading level?

DR. RUNNER: Right.

CHAIRPERSON GULYA: And that's it. Okay. All right. So, in any case, yes? I was about ready to call on you because I remember you were interested in having this as over-the-counter.

MS. HOWE: Betsy Howe, as much a listener as a participant. Through the discussion, I think it is important in addressing OSA to talk about or to put on the labeling a definition of what it is, to clearly take it beyond snoring and outline what the other problems might be for people to watch out for, and also explain who is at risk, to talk about the obesity issue, the gender issue, to clearly help people screen themselves through the labeling.

There is a second point here. Oh, and also to make referrals to organizations that might have more information. I have noted in the materials there is information from the Sleep Disorders Dental Society and the American Sleep Apnea Association, to put Web sites for those organizations so people can

get even further information.

CHAIRPERSON GULYA: Okay. Thank you.

Yes, Mr. Schechter?

MR. SCHECHTER: The question itself doesn't refer to devices that might be appropriate for OTC for snoring, but I am assuming that is included in there.

CHAIRPERSON GULYA: Yes.

MR. SCHECHTER: And a lot of the discussion this morning was regarding missed diagnosis, two words, not misdiagnosis. I think the point that came up right at the end of the morning session that such a large percentage of the population snores and a subset of them have sleep apnea, that I think, rather than this over-the-counter use of some of these devices for snoring being an opportunity for missed diagnosis, it is actually an opportunity to educate that population.

I have no evidence to back this up, but I would venture that a very large majority of people that snore don't do anything about it. And if there were products on the market OTC that were sufficiently

safe, obviously, for their use, I think here with this labeling is our opportunity and the FDA's opportunity to require manufacturers to put information about sleep apnea in those so that people become aware that this is a problem and that the fact that they snore is a large predictor of it and that maybe they should go and do something about it.

But I think the concern that by providing these devices to people is going to, in fact, cover up the population with sleep apnea, I don't necessarily agree with that. I think it is actually an opportunity in the other direction.

CHAIRPERSON GULYA: Okay. Point noted. Okay.

Mr. Crompton?

MR. CROMPTON: Yes. I would tend to echo Dan's comments there. By and large, I think that is what we have seen in the United States as we have gone over the counter with a lot of and even direct to consumer advertising. We are seeing a lot more interaction with physicians. So I am very comfortable that FDA knows how to write restrictive labeling or

impose it on us as sponsors.

I think adequate contraindications and precautionary statements could be put into the labeling for these OTC indications. I am not going to comment specifically on devices, but even some of the ones that we discussed this morning that were kind of out of hand thrown out, there was some evidence of efficacy. And even if the percentage were 46 percent, that is 46 percent better than nothing.

I would like the panel to offer some guidance to the agency in terms of the kinds of things that as clinicians, you would like to see if, in fact, some of these devices could make it OTC for snoring and then perhaps mild to moderate OSA. I think that helps the agency when they are dealing with sponsors because sponsors will continue to come in with these applications.

CHAIRPERSON GULYA: Sure. Yes. I think we will focus on the labeling issues now. And then question number 3, of course, is what the study design would look like. I think that will also provide some useful guidance for the FDA.

Dr. Rosenthal?

DR. ROSENTHAL: Yes. I was wondering if the panel could give the division some of the signs and symptoms that should be written in the labeling to tell a patient who has bought something OTC for snoring, that he or she may, in fact, have something that is more serious.

CHAIRPERSON GULYA: Dr. Mair?

DR. MAIR: I think it is better, instead of the panel to reinvent the wheel, let's go back to one of the articles here from Sleep. It goes over the AASM. The task force was specifically asked the same question you are asking.

The features, the cardinal features, are choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration. These are relatively well-written for the lay person to understand that without the medical type terms.

CHAIRPERSON GULYA: Okay.

Dr. Terris?

DR. TERRIS: Or no symptoms. So I would

say if you are snoring and no other symptoms, you may still have sleep apnea and, therefore, should see a physician.

DR. ORLOFF: Lisa Orloff.

CHAIRPERSON GULYA: Dr. Orloff?

DR. ORLOFF: Also, things that aren't necessarily symptoms of sleep apnea but would increase your risk. If you're obese, if you have hypertension already, your risk of undiagnosed sleep apnea may be higher or the consequences more severe. So those things that would aggravate the diagnosis.

CHAIRPERSON GULYA: Okay. I was also thinking that in terms of product labeling, we would want to consider things that we have recognized as adverse effects of some of these devices. How would we write things like, "Your jaw might be moved too far forward? You might have dentition problems?" That ilk of issue I think would need to be noted to the potential consumer if they are going to be starting to use these devices.

Would we want to have the FDA include something to the effect like "A regular dental

evaluation"? So that would seem to be one thing. Especially after Dr. Demko's presentation, that would seem to be primary to have a dentist check you periodically, although, again, there may be a little bit of self-contradiction here.

People are trying to treat themselves without going to a doctor. And then we're telling them, "Well, you had better go see a doctor anyway." So that may be a little bit inherently contradictory, but it, nonetheless, is probably a good piece of advice that they should have somebody monitor this. It would seem also important to tell them that these changes may take place without them being aware of these changes.

So irrespective of noticing anything, you may wish to have follow-up, particularly, Dr. Demko, would there be a time limit, say, "If you use this device for more than six months, please be aware of these certain dental changes for which you would require possible treatment"?

DR. DEMKO: Or orthodontics or surgery. I think you should --

CHAIRPERSON GULYA: I'm sorry. I can't quite hear you.

DR. DEMKO: I would say that you should tell them they require either orthodontics or surgery to correct the situation, that once it gets beyond six months to a year, these are permanent changes.

CHAIRPERSON GULYA: Okay. So anything else? I think what we are talking about here will pretty much go for the tongue retaining device, the mandibular repositioning device, and the palatal lifting device, although perhaps with the palatal lifting device, there may be issues regarding potential aspiration of portions of the product, palatal erosion, and inability to tolerate the device, period, that may need to be listed on the labeling.

Am I missing anything there? Anything else anybody can think of there? Yes, Ms. Howe?

MS. HOWE: Betsy Howe. I just noted a couple of things. One, because most of these people are older or elderly, that it needs to be mentioned that it could harm restorations or that it needs to be placed over -- is it natural teeth, edentulous teeth,

and certainly again using lay terms wherever possible.

CHAIRPERSON GULYA: Okay. Great. Thank you.

Dr. Woodson?

DR. WOODSON: Some of these things that are already prescription-approved and some of them over-the-counter, it may be that some of the things we're coming up with in the labeling are actually already on the label. Are those labels available for us to see?

CHAIRPERSON GULYA: Dr. Mann?

DR. MANN: I'll pull them up. We do have some of those available.

DR. ORLOFF: While Dr. Mann is doing that, maybe sort of --

CHAIRPERSON GULYA: Dr. Orloff?

DR. ORLOFF: A question for the fact that we know that sedative medications and alcohol increase snoring and sleep apnea and may be a comment to the fact that these devices may be less effective in the setting of sedating medications or alcohol.

CHAIRPERSON GULYA: Okay. While Dr. Mann

is, is there anything else there that anybody can think of?

DR. MAIR: Also, there are other things that can be associated with --

CHAIRPERSON GULYA: Dr. Mair?

DR. MAIR: I'm sorry. Dr. Mair.

CHAIRPERSON GULYA: Since we're jumping around a little bit, we'll give the transcriptionists a little bit of a break by telling them who we are.

DR. MAIR: Just because someone has sleep-disordered breathing doesn't mean that they have snoring or obstructive sleep apnea. There could be central causes insomnia and things along those lines. Again, it goes back, it points back to see your doctor.

CHAIRPERSON GULYA: Right. Okay. So Dr. Mann got the labeling conditions here.

DR. MANN: Just briefly to highlight what has been used for snoring pillows, as you will recall, ten years ago, the decision was made to exercise regulatory discretion. And as long as a sponsor agreed to the following labeling conditions, they did

not have to come in with a 510(k). So labeling conditions are that there can be no other medical claims made within the labeling for a snoring pillow.

The warnings that are specifically stated are that the user should consult their physician for evaluation of OSA and other respiratory disorders if your snoring is accompanied by periods of not breathing, as observed by bed partners; awakening short of breath; choking; or gagging; and certain medical conditions that had been listed as contraindications, again stemming back from the early 1990s, when this was drafted; history of heart disease; being substantially overweight. And there has been a notation that these are not to be used in infants or children and to discontinue use if there is pain or discomfort.

So, again, this was crafted many years ago. And if there are additions or alterations, we would be very interested in hearing your opinion.

CHAIRPERSON GULYA: Okay. Dr. Woodson?

DR. WOODSON: Dr. Woodson. In terms of using this as something for education, this is where

we could put in not only you might have sleep apnea, but sleep apnea is bad because it puts you at risk for hypertension, heart disease, you know, sudden death.

CHAIRPERSON GULYA: Exactly. I would think that would be an opportunity, also with respect potentially to a Web site listing.

I guess one has to think also about how much volume of material you can put on a label before somebody doesn't read it at all because if it's manageable, they might actually look at it. I think if you start giving them 15 pages of material, then they aren't going to look at anything.

That is my bias. I would be interested to hear other individuals address this and see what we would -- yes, Dr. Terris?

DR. TERRIS: One of my concerns is not just the health of the person who has the snoring or potentially sleep apnea, but it's the health of everybody who is driving on the roads with that individual who may have significant sleep apnea.

I don't know how to word that in a label but maybe something acknowledging that, hey, if you

are sleepy, you shouldn't be driving. You should pull over. I don't know if that is appropriate for this label, but to me, that is where it starts to impact everybody in this room, not just the person that has the problem.

CHAIRPERSON GULYA: I understand. Dr. Calhoun, I saw your head moving there.

DR. CALHOUN: Yes. There's just not a really good correlation between subjective sleepiness and objectively measured sleepiness like by the Multiple Sleep Latency Test or something like that.

So I agree with Dave. It's a big concern, the sleepy driver or the sleep-impaired driver, but to rely on people's self-assessment is not going to be very helpful.

CHAIRPERSON GULYA: Right. Okay. I understand.

Dr. Mair?

DR. MAIR: I would just ask a question to Dr. Mann. For the snoring pillows, now they are over the counter for mild obstructive sleep apnea. What does the labeling say about obstructive sleep apnea

presently for mild obstructive sleep apnea, specifically on the label for the lay public?

DR. MANN: The labeling is essentially very similar to what is described here aside from any kind of use issues as to how to use the pillow. The same warnings regarding the signs and symptoms of obstructive sleep apnea are listed as well as the contraindications.

DR. MAIR: But, Eric, now we are saying that we can use it over the counter for mild obstructive sleep apnea. How do you explain mild obstructive sleep apnea when we really as physicians can't get a good handle on it? How is that presently being explained as an indication for that?

DR. MANN: Yes. It's not being explained within the labeling per se. That clearance was based, as I said before, on the clinical data that was submitted, some of which is public, some of which is not. And basically the review of the product use instructions, the risk-benefit ratios associated with use of the pillow, demonstration that it was effective in reducing the RDI and so forth.

So I think it's pretty obvious that a person isn't going to be able to find out their own RDI. It was felt that there is enough of an overlap between snoring and mild OSA symptoms. That distinction, as you have noted yourself, is not always clear on the basis of the sleep studies that we have right now. And we have this history of safety with snoring pillows per se.

So I guess basically the intention was that the warnings for the one would kind of be appropriate for both in terms of the signs and symptoms that could be --

DR. MAIR: That said, if I were a company and I had an indication now for over-the-counter for mild apnea, I would want to say, "I have this indication. The other ones don't," I would think.

So you're saying that's not being done, that it's basically the same thing up here as saying no other medical conditions; for example, OSA and --

DR. MANN: Oh, I'm sorry. Yes. It does not say, "OSA," obviously, because it hasn't been cleared for that per se. But the warnings and

contraindications sections are the same.

DR. ROSENTHAL: Dr. Mair, we would appreciate any comments you have about labeling for these OSA: mild, moderate, severe.

DR. MAIR: This is Eric Mair. My personal feelings on this are that we are entering Pandora's box with very, very murky water. When we can't understand or have a good grasp on it, I don't think that the public will have a grasp at all.

If I see that there is an indication for obstructive sleep apnea as a consumer and I look at the labels of tongue retaining devices, nasal dilators, mandibular support devices, that's only for snoring. But, hey, this pillow works for apnea. And I will have no --

DR. ROSENTHAL: The mandibular devices are for moderate.

DR. MAIR: Okay. They are support devices. I guess they aren't for anything right now.

DR. ROSENTHAL : No.

DR. MAIR: But if I look at what is out there now as a consumer, my concern is that I have not

seen the data. Where is the beef? And I know that you're telling me it's out there, but if it's not out there, if we can critically review that and --

DR. ROSENTHAL: But do you have any suggestions for labeling in this area?

DR. MAIR: My suggestion is from what I have seen -- and I have been through the literature quite extensively on these snoring aids -- I don't see an indication for over-the-counter for mild obstructive sleep apnea for cervical pillows. I think it would be more in line with the FDA policy and as a consumer advocate to keep these -- I think David was saying -- sort of together and to take that indication off.

CHAIRPERSON GULYA: I think what the FDA can get --

DR. ROSENTHAL: You don't want to help us.

CHAIRPERSON GULYA: -- from us is what the labeling is. I think the decision has been made and would be I think virtually impossible to unmake at this point in time. So I think what we could do to help would be to give language that would mitigate the

potential harm to the unwitting consumer. And that would probably be the most productive way to proceed.

So I guess other than strongly encouraging an individual to seek medical attention or --

DR. TERRIS: David Terris. I think they've hit the major ones that most of us would agree are best indicators of sleep apnea. So I don't think there's anything more to be said, I think, from a sleep medicine standpoint.

DR. MAIR: Eric Mair. From a labeling standpoint, we know that the mortality statistics show that an AHI showing severe apnea is associated with increased mortality. We know nothing about mild and moderate.

Why are we going through, "Yes, we'll approve it for mild but maybe moderate and then severe"? The strong statistics at least from my read, even including with hypertension, with CVAs, et cetera, differentiate severe apnea from --

DR. ROSENTHAL: That seems to negate the whole issue, then, of not allowing over-the-counter devices for mild sleep apnea.

DR. MAIR: Exactly. What I'm saying is --

DR. ROSENTHAL: So you're saying we can allow devices for mild sleep apnea because there are no serious consequences.

DR. MAIR: No. I think that either it's for apnea or not for apnea. As a consumer, as someone out there not a physician reading and I have apnea, most people I don't think know.

My patients who see me in my sleep disorder clinic who are well in touch with their obstructive sleep apnea and may know their AHI won't know anything else about their sleep study. And the usually don't know the category that they're in. Then it goes back to, "Why are we doing over-the-counter for mild and moderate apnea?"

I can understand for prescription because the physician who knows can separate mild, moderate, and severe, but for an over-the-counter application, I think it's murky water.

CHAIRPERSON GULYA: Well, we still need to think about labeling. I have one proposal. And you can shoot it down, but it's going to be thrown up

there for discussion. That is something to the effect that this product should not be used as the sole component in the management of mild OSA. It should be used only as part of a complete therapeutic regimen under the care of a doctor.

Now, I understand we cannot reverse the wheels of time in terms of approval of something being OTC. I would like to clarify. We can add labeling things onto something. So I would like to hear some discussion about that as an idea.

I will not be wounded if you think it is a perfectly horrible idea. I just want to get something so we go productively into saying, "What can we do with the labeling with things as they are to adequately help the consumer use this product and not do themselves harm, taking into account all of what you are saying?"

I totally hear it, but, unfortunately, we're not in 1992. We're in 2004. And we just have got to work with the clock. Let's go first with Dr. Calhoun and then Dr. Terris.

DR. CALHOUN: Karen Calhoun. Yes.

CHAIRPERSON GULYA: Thank you.

DR. TERRIS: Yes. I was going to say I like it. It sounds good.

CHAIRPERSON GULYA: Okay. Anything else we can think about? Anybody else have any objections or "Attaboys" or anything like that for me?

DR. ORLOFF: Attagirl.

CHAIRPERSON GULYA: I even wore a skirt today, too.

So I have the feeling that we have really almost beaten this to death here with the tongue retaining device, the mandibular reposition device, and the palatal lifting device.

FDA, are we all square with you on this? Anything else we can address here with this?

(No response.)

CHAIRPERSON GULYA: Okay. Now, in terms of the nasal dilators and cervical pillows, we already addressed the cervical pillows. Anything for the nasal dilators that we think should be added to the product labeling? Do we think that is all right? They are already over-the-counter. So I guess what we

can do is just -- do we have the --

DR. CALHOUN: Do they have the same labeling that we see up here?

DR. ROSENTHAL: That is the --

CHAIRPERSON GULYA: Actually, no. It's in Dr. Mann's presentation, page 3, the top slide. He had "FDA Policy: Nasal Dilators. Labeling Precautions and Warnings."

DR. MANN: I would just emphasize that these have been cleared for snoring OTC but they have not for OSA, mild or otherwise.

CHAIRPERSON GULYA: Right. It's right up on the slide. And what is the recommended duration of use?

DR. MANN: It depends on the individual device. You saw many.

CHAIRPERSON GULYA: Okay. All right. Anything we can add to that?

(No response.)

CHAIRPERSON GULYA: Okay. I see nothing there. Cervical pillows I think we have pretty much covered. Mandibular support devices I think everybody

--

DR. TERRIS: I'm sorry. Julie, can I go back?

CHAIRPERSON GULYA: Sorry. Sure. Dr. Terris?

DR. TERRIS: Dr. Terris. I just realized that there's no mention on these warnings that if you have associated conditions like high blood pressure -- I forget what the other one said. It might be useful to add that here as well because we know that even snoring is an independent risk factor for hypertension.

CHAIRPERSON GULYA: Okay. Point well-taken. I see that being written down there. Now, as I recall, with respect to the mandibular support devices, we all felt that there was insufficient evidence to declare OTC one way or the other. So I think I will probably agree with Dr. Suzuki here and say that is a moot point for discussion.

So I think we're actually doing quite well with time. It may be that question number 3 does have

a little bit more in the way of challenge for us and a little bit more room for discussion because here is where we get into the meaty issues of "Okay. What kind of studies do we want to see and what is the manufacturer going to have to provide in order to market these devices for snoring and/or obstructive sleep apnea?"

So let's start off with the first one. In terms of general clinical study design, including control group and whether or not you think a control group is needed. Who wants to lead off? Dr. Mair?

DR. MAIR: Usually, the simplest study designs for treating snoring devices that can be used across the board once they're cleared is a crossover-type study, where the patient can serve as his own control.

The problem with crossover studies is we have to make sure that there is a sufficient washout period in between. And that could be difficult for, let's say, the mandibular repositioning devices when you know there might be some changes in the patient's anatomy afterwards. So they're not really serving as

their own control afterwards.

I think the important thing to look at this is to see, is there a sufficient washout period? And I think the controls are necessary if you used a parallel philosophy of treating patients and controls separately.

That's usually very difficult from a company point of view. You will need more patients involved. And I think it is very meaningful for patients objectively and subjectively to see if one device works, even versus another, and may make it serve as their own control.

CHAIRPERSON GULYA: Okay. Dr. Terris?

DR. TERRIS: I'll take a different tack. I don't think controls are necessary because there's not really going to be a placebo effect in terms of evaluating the sleep apnea. So I would say the patient is their own control.

Now, if you want to compare it to another device and study it down the road, then I would agree with that statement. But otherwise I would say no control necessary. Preoperative or pre-intervention

polysomnography. Intervention, post-intervention polysomnography. And that would satisfy me at least. I wouldn't need a control group.

CHAIRPERSON GULYA: I have a question. This is Dr. Gulya. I mean, what I heard was there was considerable variability in the polysomnogram, that somebody could have a highly abnormal, putting them into moderate to severe obstructive sleep apnea one testing session and then the next testing session, they might be mild or moderate.

The other thing I would worry about is, how are you going to control for regression to the mean? If somebody picks a severe OSA candidate for testing, I mean, what do you know is going to be just the likelihood that that cohort is going to exhibit some random improvement that we will attribute inappropriately to the device?

So I guess one measure that would address those issues would be, what kind of baseline are you going to pick for your testing? Are you going to take one polysomnogram? Are they going to have a couple? And my understanding is patients aren't real happy

about going through one, much less multiple ones. So how do you pick what is a stable polysomnographic result? I was kind of struck by that.

DR. TERRIS: Yes. Well, I guess I thought we were doing this one item at a time. So a control group won't address any of those issues, right? So I would say yes, these are important things we can hammer down into details, but in terms of the first issue, do we need a control group, I would say no.

DR. MAIR: He serves as his own control in a crossover study. Is that what you're saying, that a patient has his own control group?

EXECUTIVE SECRETARY S. THORNTON: Dr. Mair, could you speak into the microphone, please?

CHAIRPERSON GULYA: But if each patient has such variability, that's what I'm wondering. How can they be their own control if --

DR. MAIR: The problem is with variability; first of all, this "first night" effect. So that if you have the patient get a sleep study and then have the treatment and then another sleep study afterwards, you are going to worry about the first

night effect.

The other thing is that probably this is a very useful place for home sleep studies, especially those that measure snoring and apnea, because that is where the patient really sleeps. Many times in a sleep lab, as most of us know, the test is measured on your back, and you almost have to lay on your back. And many times we don't do that or many people won't do that.

So to get away from the first night effect, Terry Davidson had a very nice article on this looking at the first night effect for home sleep studies, when you're in your own home with very little devices on you, not like Dr. Terris looked in that one picture, poor guy, that you don't have or a negligible first night effect.

Then the other important thing is that we can't measure apples and oranges. We can't have one sleep lab measure pre and another one measure post. It has to be not only the same sleep lab or the same home sleep study, but it has to be the same person blinded, of course, interpreting the results.

There are different ways of measuring an AHI, as we alluded to in here. "Hypopnea" is an extremely variable term. And whether it's measured by the saturations going down 4 percent and holding breath for 10 seconds, about 50 percent airway obstruction or can be measured by EEG, looking at arousals.

And strictly looking at arousals, there are two basic criteria: The Medicare criteria and the Chicago criteria. Many sleep labs use variations and perturbations of these.

So whatever we measure, we have to measures apples and apples. I think that the home sleep study is the best way to go on this because you don't have the first night effect.

And I think that a patient serves as his own control for snoring, let's say, that you can measure the snoring with an in-home sleep study. And then you can apply the device and then after an appropriate period of wearing the device, to then get another sleep study.

You also need subjective data. Does the

patient when they have had their sleep study have more alcohol that night before or did they have an upper respiratory infection before either one of these? They can all be measured and have been done in multiple studies where we have to look at the potential predisposing factors, such things as nasal obstruction, et cetera.

CHAIRPERSON GULYA: Dr. Terris?

DR. TERRIS: So to address something that you said, Julie, which patients to study, I would say what indication they want. So if they are looking for mild sleep apnea, I would say the patients must fit into that category. I wouldn't be in favor of approving it for one indication of a severe case when they have had studies that were done in mild patients and vice versa. So that answers that question, at least in my mind.

CHAIRPERSON GULYA: Okay.

DR. TERRIS: In terms of the first night effect -- and I would differ significantly with my colleague, Dr. Mair, my esteemed colleague, Dr. Mair, that we should --

CHAIRPERSON GULYA: The gentleman from Wilford Hall.

DR. TERRIS: -- that we should favor ambulatory polysomnography. Even though I'm a proponent of it, of ambulatory, because it will increase access and get more patients through the door, when it comes to validating a device that is going to treat a patient with this disease, I would not want to rest on ambulatory polysomnography. And, again, I am sure I can speak for my sleep medicine colleagues because they would feel the same way.

The first night effect exists, no question about it. But because of the way it works, if anything, you are going to underestimate the effect of your intervention because what happens is if a patient is uncomfortable with all of this stuff on, they don't sleep very well. They don't get into the deeper stages of sleep. So it tends to underestimate the severity of their disease, which is why many sleep medicine folks say everybody needs not a full night study, they need two nights or three or four nights of sleep study to really characterize their disease. And

obviously that's beyond what we can realistically provide.

But for a study validating a new device or a device, I would say attended in-hospital polysomnography is what it is going to take me as a reviewer for a manuscript. For reviewing for Laryngoscope, you know, I want to see an attended study just to approve a manuscript, let alone a device to be approved by the FDA. And because of the way the first night effect works, I would be comfortable because, if anything, it is going to underestimate the effect of the device.

So I would stick with attended studies. I would characterize the patient population according to the indication that they are trying to achieve and, again, no separate control group.

CHAIRPERSON GULYA: Dr. Mair, one last comment here. And then I think what we will do is move on to B. And we'll get more people involved. I might start calling on individuals.

DR. MAIR: Just some thoughts again for my esteemed colleague, Dr. Terris. The first night

effect if it doesn't have that much to do, it will underestimate the snoring anyway. Then there might be an effect of the snoring aid that we're missing by doing these controlled studies with an in-house polysomnogram and measuring the first night. So we might be missing a device that really does work and will help patients based on the false results from the first night effect. Multiple night sleep studies.

This is the best way to go. There's no question. And to do in-house polysomnography and get over the first night effect with multiple nights is extremely expensive. At-home portable multi-channel sleep tests are very inexpensive for multiple nights. It can be used for multiple nights, and this should be recommended.

As far as validation is concerned, this is a very important, a crucial point. There are several home multi-channel sleep studies that have been validated and strongly validated. Of course, those are the ones that we should use.

There's a market out there for multi-channel sleep studies just like for snoring aids

and anti-snoring devices. They vary from one side to the other.

We ought to look for the ones that have been scientifically validated and published in peer-reviewed journals, which there are several. And we ought to look toward those to get our significant data.

DR. LI: Julie, can I make a comment?

CHAIRPERSON GULYA: Where is that coming from?

DR. LI: Right here.

CHAIRPERSON GULYA: Yes, Dr. Li. Sure. Sorry. Thank you.

DR. LI: Kasey Li. I think it's well beyond the scope of this Committee to talk about the definition of hypopnea, the interpretation, and types of sleep studies that we're using.

I would agree with Dr. Terris in that any studies need to be up to the standard of what is currently accepted as the gold standard of evaluation, which is attended in-house sleep study.

CHAIRPERSON GULYA: Thank you very much.

Any other comments? Dr. Jenkins? I was waiting for you.

MEMBER JENKINS: I can't accept an efficacy study without controls. You can't say that this is working unless you have got a control group there to compare it against.

I'm not sure where you're coming from saying you don't need a controlled study. Particularly if you've got a 30 percent error rate here in the test/re-test situation, you have to have it controlled. You've got to be doing the same thing showing that one has a 50 percent change, the other has a 20 percent change. That 20 percent change is within your 30 percent reliability.

You know, you can't just say, "Yes, this is efficacious" without having your controls to show that.

CHAIRPERSON GULYA: I saw Dr. Zero nodding his head. So I'm going to put him on the spot and have him throw in his two bits' worth also.

MEMBER ZERO: Yes. Although again this is not my area, running research without a proper control

to me sounds so foreign that I don't understand it. I understand the limitations in certain areas that you have because of costs or feasibility, but science is science.

And the best design I have heard so far is Dr. Mair's design, which would be what I would call a randomized crossover design, where you randomize the order of entry into the study, you understand the carryover effect, as was described, and you limit the length of the study so you don't cross over that six-month period where you get irreversible effect and you can't recover those.

So to me that is the best design. The issue of what I would call a lead-in to the study, which is basically the overnight stay, also makes sense for me as an uninformed observer, we'll say, for this type of research because, again, if you are looking at the effect of something, you don't want to know what the effect is in a pure research sense. You want to know what the clinical effect is. And if you have the overlay of being your body surrounded by sensors and various paraphernalia, you have to get

tolerance to that so you can actually get a true experimental effect that means something clinically. So I am strongly supporting some of the discussion here.

CHAIRPERSON GULYA: Okay. Mr. Crompton?

MR. CROMPTON: I would say for device trials, though, there is a long history exactly as Dr. Terris is pointing out, where subjects do serve as their own controlled cochlear implant studies. Most orthopedic studies are designed that way.

I liked the logic. Obviously there is a cost factor here of Dr. Terris' presentation, where the subject could serve as his or her own control. I think these studies have been well-received. It's not the classic design. But for device trials, they are very different than drug trials.

CHAIRPERSON GULYA: All right. Comments?

DR. TERRIS: You first, Kasey.

CHAIRPERSON GULYA: Dr. Li?

DR. LI: Well, you know I am going to agree with you.

(No response.)

DR. TERRIS: That's why I let you go.

DR. LI: That's why he was going to let me go first.

CHAIRPERSON GULYA: He's got a big grin on his face.

DR. LI: Obviously we want to have as rigorous a scientific approach as we can, but with the currently accepted, what I could extrapolate from is really the surgical literature on the treatment of sleep apnea. And all of the surgical literature relies on the patient serving as their controls.

That is the first issue. The second issue is the night-to-night variability, if you really look at the published literature, I think the 30 percent is an outlier. Mostly accepted is about 15 percent in terms of night-to-night variability if we look at all of the published reports.

So that's it.

CHAIRPERSON GULYA: Okay. Dr. Terris?

DR. TERRIS: Dr. Terris. And just so nobody leaves here thinking I am not a good scientist, there are two. You just heard what Kasey said. There

are only two prospective randomized trials controlled for the surgical treatment of sleep disordered breathing, and both of them are mine. So I understand the value of science, but --

DR. LI: Actually, that's incorrect, David.

(Laughter.)

DR. TERRIS: But despite that, despite that, for validating a device -- and I do over the years a fair number of studies looking at different devices. It's prohibitively expensive. I mean, you want to have a control group. You want to have multiple nights of studies. You're talking about thousands and thousands and thousands of dollars. And talk about not getting the product out to the consumers that need it. Holy cow. So it's just not realistic.

And there's no placebo effect. I mean, it just doesn't make sense in this condition.

MEMBER JENKINS: But to get a device out to the public without having these trials, it's billions of dollars in lawsuits and that sort of

thing, too. So you can't really look at it that way. You've got to show that it's efficacious in a good, scientific manner.

DR. TERRIS: I agree if it's necessary. If it's necessary to have a control group, you should have them.

CHAIRPERSON GULYA: Dr. Zero, please.

MEMBER ZERO: In an uncontrolled study, there is something called experimental bias, which is the investigators themselves who want to show a treatment effect.

This is well-documented in every form of research. So I don't know how you get away from that point without a control.

CHAIRPERSON GULYA: Right. Okay.

DR. TERRIS: Can I just respond to that? Let me just respond to that specific point. This is Dr. Terris because the person who is running the study is not the person who does the sleep study. So it's a different individual. That gets around that issue, but that's a very good point. You have experimenter bias.

CHAIRPERSON GULYA: Are we happy here? Have we addressed this issue well enough for you?

(No response.)

CHAIRPERSON GULYA: Okay. Good. All right. Next we will move on to before we come to blows -- I don't know who I would bet on right now at this point -- the endpoints which would be acceptable for the assessment of the effectiveness of treatment. Okay. Let's see. I would like to hear from -- let's go with Dr. Suzuki.

MEMBER SUZUKI: I've got a couple of things. I'm not a behavioral scientist either, but there are probably a couple of different measures for endpoint that at least I can see from a dental standpoint.

First of all, with respect to endpoints on the mandibular repositioning devices, is it okay to cover those also?

CHAIRPERSON GULYA: Yes. I think we can just throw these all in the pot, just general study design issues, I think.

MEMBER SUZUKI: Okay. I would suggest

serving as appropriate endpoints consideration of a dental arch alignment examination, pre and post; determinations of occlusion, pre and post, even using an articulator. And hopefully there will be no changes pre and post. I don't expect improvement, but no changes is what I would expect to see as an endpoint. Also, a soft tissue exam, pre and post, to provide that there are no untoward reactions against soft tissues with these appliances.

From a behavioral standpoint, measurement with a questionnaire, either self or with a spouse/bed mate. And I'm not sure how you would design it, but behaviorists would probably make a simple ten-point questionnaire. A TMJ evaluation to make sure there's no adverse effects on the TMJ and, of course, any appropriate electronic evaluations of electromyography or other substance also indicating that there are, in fact, no changes using these devices and, in fact, perhaps even improvement. So those are like four or five that I could consider as endpoints.

CHAIRPERSON GULYA: Okay. Dr. Zuniga?

MEMBER ZUNIGA: John Zuniga. One other if

I can go back to some of the last discussion quickly. There is also some subject bias, I think, in subjects who return constantly over and over time. Hose patients may do better, better, better for the experimenter. So an ongoing clinical trial, that's why the importance of a control group exists.

I would recommend an equivalence study for these OTC devices such that the comparator be some gold standard within the known published literature, for example, the mandibular protrusion devices be compared when using the over-the-counter devices, that the primary endpoints be defined.

Obviously depending on the object of the study if you're looking at OSA, that's a different group of patients that looking at snoring and then the various intensity levels of the OSA group, second endpoints being those criteria or substances, secondary problems, snoring, and et cetera.

I would like to know about the duration of effect of these treatments. Once you stop the treatment, how long do the positive or negative effects persist or go on?

CHAIRPERSON GULYA: Okay. Thank you.

Dr. Demko, I would be interested in hearing your thoughts on this, particularly from your presentation. You clearly have seen a broad gamut of some of the outcomes here.

DR. DEMKO: Gail Demko. Certainly there's no more than a two-day effect. It's like CPAP. Once you stop treating a patient, the effect goes away. The snoring comes back. Usually there's one day they're a little bit better and then all gone into.

With the oral appliances in general, the washout periods have been anywhere from two to four weeks. So if you're within that first six-month period where things are not permanently moved, almost always they will go back to where they were. Edema will resolve in the joint.

The only thing that I have ever had trouble with on patients is where they do have shortening, what is probable shortening, -- we don't know for sure -- of the internal pterygoid bringing the mandible forward after long periods of time of edema in the joint. So I have patients. Most of them

are intermittent appliance users after they start running into trouble.

I think that using patients as their own control really has been where we have been, but if you look at the critical evaluation article that was mailed to us secondarily, they were just very unimpressed with most of the studies that have been done with oral appliances to date.

CHAIRPERSON GULYA: And in terms of endpoints for the effectiveness assessment?

DR. DEMKO: Endpoints, the effectiveness, it takes almost always three months for a patient who is self-titrating, moving the mandible forward before you get to a truly effective position. The more slowly they move themselves forward, the further they are going to be able to go, the more effective the appliance will be. The further they go, the more side effects they have.

So most of the studies will stop short of six months because that is why it is just now -- Alan Lowe developed the Klearway appliance in 1995. He is just now getting together five-year data on

appliances, even though he has been using them for almost ten. That will be published this next year.

So we are seeing significant changes. It is all within the last two years that all of this data has come on for long-term use, even though we have been using appliances since 1983.

CHAIRPERSON GULYA: So in a study if a manufacturer were to propose some sort of mandibular repositioning device, would you want to see as a requirement presentation not only of six-month efficacy data but also of one-year or one and a half-year complications or adverse effect data?

DR. DEMKO: Only if he were going to try and advertise that he had less of a problem than others on the market. Otherwise, in my hands over two or three thousand patients, they are all the same. They all do the same damage.

So it is only if he was going to try and prove he was better or say he was better, he'd better prove it.

CHAIRPERSON GULYA: Okay. Dr. Calhoun, any thoughts on some of the endpoints?

DR. CALHOUN: I think there are the things that we look for in any study: a change in RDI, change in minimum O2 saturation, maybe changing in snoring loudness. We might want to look at some of the secondary things, such as some of them somewhat subjective: headaches, cognition, hypertension, maybe even performance of complex tasks.

CHAIRPERSON GULYA: Okay. How are we doing on question B? Are we good there? Anything that is remaining outstanding?

(No response.)

CHAIRPERSON GULYA: Hearing that there is a nod of the head that everything seems to be copacetic on the FDA side, we will proceed along to question number C. Now, this is an interesting one, the degree of improvement for each of the endpoints which would be clinically meaningful assuming an acceptable adverse event profile. Who would like to tackle this one? Okay.

MS. HOWE: This is Betsy Howe. This might be going back to the previous question, but since we're talking about an over-the-counter issue, I

wonder if we could ask untrained, raw consumers to actually demonstrate proper fit of the appliance and also if there could be added into the questionnaire seeking if the labeling or the warnings are actually educating them about knowing the difference between snoring and OSA risk factors.

CHAIRPERSON GULYA: I hear you. Thank you.

Yes, Dr. Zero?

MEMBER ZERO: Just a point of clarification. With question 3, are we delating with OTC or prescription or both?

CHAIRPERSON GULYA: Well, I was taking these as OTC. That was my understanding from FDA. And I am seeing a nod of the head. So this is for OTC application.

MEMBER ZERO: Okay. I just had that question almost going in. And I appreciate the clarification.

CHAIRPERSON GULYA: Sure. No, no, no. It's always better to ask and make sure. I understand. Absolutely. So what are your thoughts?

MEMBER ZERO: Thank you. Good segue. Again, in trying to understand the issue of these endpoints, to me they seem to be a catch-all of everything you can do, but I'm not clear if it's everything you should do.

CHAIRPERSON GULYA: Well, also I was reminded that the FDA has to have this concept of the least burdensome approach also. So I think we need to go for, as Willie Sutton said, where the money is. Where do you think the biggest --

MEMBER ZERO: Well, that's exactly where my question is going. In this gold standard of the -- what's the term? -- polysomnography, there are a number of different outcomes. I am assuming there have been validation studies done over several years and that this is the gold standard because it stood up to validation.

If that is not the case, then I think we need to look at that and say, does one of these indicators give you enough indication of where you really need to go? Because the cost both from the clinical management of this point of view as well as

from the research design point of view, the cost seems to be almost prohibitive to doing what you need to do.

So my point is maybe this has already been discussed, but what is the validity of these? I heard the term a "tarnished gold standard." Does everybody agree with that term or is this really an accepted approach?

CHAIRPERSON GULYA: And we need to address also what is a clinically meaningful change also because you do a --

MEMBER ZERO: Well, validation at the clinical level. That's what I am pointing towards.

CHAIRPERSON GULYA: Okay. Dr. Woodson?

DR. WOODSON: There's also a difference there. There's a certain clinically valid meaningful endpoint for us on a panel trying to decide whether or not something is approved but also the information that you put in the products so that the patient can decide whether or not they are going to spend their money on this. So that is the kind of data that has to be collected, too.

So it's going to be completely different

for snoring than for sleep apnea. For snoring, you could say a "such and such decibel rating," which you measure there, where there are also some acceptable rating systems by the bed partner. You can say the bed partners felt like it was reduced, the snoring was reduced, by this much.

CHAIRPERSON GULYA: Okay. Dr. Mair?

DR. MAIR: A little phrase I have heard. Eric Mair. "Snoring is in the ear of the beholder." That is very true in that most of the studies that measure snoring are subjective in nature. However, we do need to get beyond that and look at objective data.

The standard definition of success as far as from snoring, the standard definition should be that there is a subjective improvement. The bed partner is happy, uses a VAS scale 1 through 10. They put a little X on there, easy to do, inexpensive to do.

And the other is an objective test. There are some problems with some objective tests measuring decibels because you have a microphone hanging. Then the patient rolls over, one side or the other. It is

going to drastically change. So usually it is wearing an oronasal like a little oxygen and little catheter and then having the microphone in that area. And that measures decibels. That is still very relatively inexpensive.

CHAIRPERSON GULYA: How much of a change is considered clinically meaningful in the terms of the decibels?

DR. MAIR: The decibels you are looking for a change of the -- I have that written specifically down, but there are different ways of measuring sound on decibels from an oronasal. There are acceptable standards. I could include those in --

CHAIRPERSON GULYA: Is it like a 50 percent reduction or 75?

DR. MAIR: No. There are about 4 or 5 different things. It's bringing the one threshold, maximum threshold, five-decibel change. But I have that written in here, and I could give that to say that.

The second thing, though, there is a definite success story for obstructive sleep apnea, at

least what is a standard acceptance. And that is that the AHI goes to a physiologic level; in other words, AHI less than five. That's a complete success.

And then we have the partial response or partial success. That is a satisfactory improvement of the symptoms with a 50 percent or greater reduction in the AHI. Of course, that is also assuming that AHI is below 20 because this is associated with the increased mortality that we talked about before.

So I think that is a standard thing. And it is in our article here that we were given. And that is used in I think most studies, and that is not difficult or expensive to do.

CHAIRPERSON GULYA: Dr. Li, point/counterpoint?

DR. LI: Well, I think it is reasonable to use the RDI in terms of less than 20, but less than 20 is moderate sleep apnea.

DR. MANN: I'm talking about a partial response for that, Kasey. This is Eric Mair. The complete response is an AHI less than five, but you can't just say a complete responder or no responder.

I think that would be unfair. And most studies now look at this as having either a complete response, a partial response, and then less than partial is considered a no response

I agree with what you're saying. A partial response is not a complete response, but I think it is something that needs to be measured.

CHAIRPERSON GULYA: Okay. Dr. Li?

DR. LI: Well, one other issue is if you look at all of these products and specifically pointing to some of the data that has been reported in some of the articles, it is -- I hate to mention this, but is RDI an adequate assessment? Oral appliance is notorious for improvement in RDI and no improvement in lowest oxygen saturation. And that is a major component of morbidity I obstructive sleep apnea syndrome.

I don't have any answers, but I am just trying to point out some of the deficiencies in terms of the "gold standard," what we're looking at in terms of outcome measurement.

All I could suggest is what is currently

accepted, whether it's in the surgical literature or in the medical literature in terms of usually it's a 50 percent reduction in terms of the RDI.

But whether we should include lower oxygen saturation or not, I think we would have to have some leeway in terms of assessing whatever comes across the FDA, whatever the submission is, to look at the data specifically in terms of what should be looked at.

CHAIRPERSON GULYA: Dr. Suzuki, I would like your thoughts, please.

MEMBER SUZUKI: Just in our discussion of question C, I would like to just apply what my comments were in section B.

CHAIRPERSON GULYA: Okay.

MEMBER SUZUKI: And that is that the behavioral science endpoints definitely should show some improvement, whether it be spouse/bed mate and/or self-questionnaire. But also with respect to the dental outcomes, such as arch alignment, occlusion, TMJ, soft tissue changes, there should be no adverse changes in those parameters.

So for C for "endpoint" for dental, there

would be "no change."

CHAIRPERSON GULYA: So no change. Okay. In terms of the behavioral testing, how much of a degree of improvement would you think would be appropriate to take as your clinically meaningful endpoint?

MEMBER SUZUKI: You would have to ask a behavioral scientist.

CHAIRPERSON GULYA: Okay. Dr. Zuniga?

MEMBER ZUNIGA: I can't comment on the primary endpoints. Everyone else has before me. Maybe some second endpoints might provide some more insight into usefulness, such as time to onset of effect. And maybe some devices might work different than other devices, either equivalent or superior.

The other is, especially for the OTC, duration of effect; i.e., assuming that some of these materials may change over time, maybe the benefits will decrease over time or maybe they will get better over time if there is a placebo effect. And so those kind of criteria.

CHAIRPERSON GULYA: Okay. Does anybody

else have anything they wish to add to this point? Dr. Orloff?

DR. ORLOFF: Lisa Orloff. Maybe just an expansion on what Dr. Suzuki was saying, but since one of the most important things to the patient is their subjective quality of their sleep or their sleepiness score, although it is subjective and it's also prone to the placebo effect, I think that that would be worthwhile data to have, whether the patient has their own control or not, to study to measure sleepiness scores and compare between a control and with the device or even with the device, for example, the mandibular repositioning device, in place but not advanced. And so it's sort of a sham having the device on but not repositioned at all and then protruding mandible.

CHAIRPERSON GULYA: Okay. Great. Thank you very much.

Anybody else have any comments?

(No response.)

CHAIRPERSON GULYA: Okay. FDA, have we covered this for you? Do you think you have the

information you need?

(No response.)

CHAIRPERSON GULYA: All right. I see a nod coming from over there. All right. We will sally forth to D. The specific adverse events, if any, which should be carefully assessed by FDA from the clinical trial. I will have Dr. Suzuki lead off on this because I think you have been given the opportunity to iterate this for the third time.

(Laughter.)

MEMBER SUZUKI: Well, I guess I would look for a worsening of dental effects, speaking from a dental standpoint. Are there any changes in occlusion, TMJ, soft tissue status, arch alignment, things like that?

Behavioral science questions would be, is the situation getting worse statistically, at least by one standard deviation? Is my snoring worse? Are my sleep, daily sleep patterns, changing adversely and questions like that?

So those are the two parameters I would look for as adverse.

CHAIRPERSON GULYA: Okay. Actually, I have a question here. Again, this is a little bit out of my area. When we are talking about the jaw realignment issues, when we are talking about the fibrosis and scarring and the dental changes, I guess, like when you were talking, Dr. Demko, about the fluid and the TMJ, that seemed to me like a marker for there is potential trouble here.

In my incoherent way, I am asking, are there other markers for there is trouble brewing here other than just trouble starting to happen in terms of dental realignment? Is there some sort of -- do you understand what I am trying to say?

DR. DEMKO: Yes.

CHAIRPERSON GULYA: Is there some marker for worse troubles yet to happen but you can sort of start seeing things before you actually get to the point of a serious problems?

DR. DEMKO: This is Dr. Demko. And no.

CHAIRPERSON GULYA: No.

DR. DEMKO: What we do see is fluid build-up within the first month in about 40 percent of

patients. However, almost all of them have total control. And it's gone within five minutes. They get up in the morning. They take the appliance out. Their jaw is thrown forward just that fraction of a millimeter. They hit the anterior teeth. And the natural overlap of their teeth as they swallow will basically hammer the law back into its normal position.

CHAIRPERSON GULYA: Okay.

DR. DEMKO: It does not happen with people who have significant overbites, where their top teeth are well beyond their bottom teeth. Those are people who are going to have more change.

People whose bottom jaws naturally are either even with the top teeth or further forward, they're not going to have that easy resolution. It's the patients I find because for five years now that I have been seeing this, I have been neurotic about warning all of my patients that this will happen to them, even though it doesn't.

I find that the biggest jaw changes are in the men because they just go, "Yeah, yeah, yeah. My

teeth don't touch" and the women are going like "Oh, my God, my profile is going to change." So the women have a more vested interest in their own viewpoint of getting their mandible back into position within 15 minutes every morning.

I actually hand out Double Bubble bubble gum with every new appliance because it works better than almost anything. It doesn't come sugar-free. And Bazooka Joe, which does, is too soft. And bagels don't work, but going to Trader Joe's and pumpkin seeds do and cut-up latex gloves.

CHAIRPERSON GULYA: I don't think I want to go trick or treating with Dr. Demko.

(Laughter.)

DR. DEMKO: You get a toothbrush. I hand out toothbrushes.

So there are a lot of things that do happen. Most of the changes that are truly adverse that are really going to cause me conniption fits aren't going to be in the first six months. Therefore, it's just making sure that whatever is coming on the market isn't worse than what is already

there.

I do like the idea of patients saying what is going on, but as for the mobility, what I would like to add to Dr. Suzuki is I want clinical evaluation of changes in the dentition.

I don't want the patient responding. So in Glenn Clark's work, where he is looking at long-term data but it's by questionnaire because of what Anette Fransson found out, that patients aren't aware of these changes, I want that clinically documented by somebody who evaluates it using a T-scan or something like that.

CHAIRPERSON GULYA: Okay. Dr. Zuniga?

MEMBER ZUNIGA: Sorry. John Zuniga.

There are some objective outcomes you can file for all of those areas. For TMJ onset of pain, limited opening, joint sounds, those are certainly criteria that patients as well as their objective followers could evaluate.

Also, in terms of fluid in the temporomandibular joint, using the MRI, supposedly being the gold standard, there are also many studies

that have shown that you can observe MRI changes that suggest fluid build-up in the joint, even in the normal populations. So there is not a direct correlation with symptomatology and outcome.

CHAIRPERSON GULYA: Okay.

MEMBER SUZUKI: Madam Chairman?

CHAIRPERSON GULYA: Dr. Suzuki?

MEMBER SUZUKI: Jon Suzuki. As a follow-up to Dr. Demko's and Dr. Zuniga's comments, I didn't know you wanted the detail, Madam Chairman, on TMJ, but, in addition to Dr. Zuniga's comments, granted TMJ pain is certainly one of the objective outcomes you can look for as an adverse event. There are others in the pecking order of TMJ diagnosis that I think are also important.

CHAIRPERSON GULYA: Okay.

MEMBER SUZUKI: They include TMJ crepitus upon opening, for example; TMJ clicking; popping, whether it be bilateral or unilateral even. I think those are all events that have to be looked for as a worsening of a particular condition. So I would add that to possible adverse events that might be

evaluated.

CHAIRPERSON GULYA: Okay.

DR. DEMKO: I would just like to add one thing is that this year, early in this year, three articles came out showing that mandibular repositioning devices being used for obstructive sleep apnea actually had an ameliorating effect on TMJ problems, that in all of the time I have been doing these appliances, I have only had seven patients not be able to wear an appliance because of TMJ pain. All of the rest of them could if it was introduced correctly.

TMJ is almost a non-issue now for those of us doing sleep apnea.

CHAIRPERSON GULYA: Okay. All right. Dr. Zero?

MEMBER ZERO: It seems we have categories of adverse events here. Some of them are adverse events that dentists would only pick up that may be only important to a dentist. Then we have a category which would be appearance-related and pain-related, which the patient would be most concerned about. And

then we have transitory changes and then permanent changes.

Again, in structuring this as adverse events, I think we have to keep maybe those perspectives in mind because I think some of the changes, like the movement of a few microns of a tooth, may not be very important to a patient. Although we can measure them, they are clinically insignificant.

So I think we have to structure our thinking around these adverse events as what are, in fact, important to the patient and, where important, to health and not so much concentrate on what is important to a dentist necessarily. I have a dentist. So I can say that.

CHAIRPERSON GULYA: Okay. It's kind of the distinction between an adverse event and a serious adverse event. Just because something happens, there is a continuum of severity. And you want to make sure that that is recognized in the adverse event reporting.

MEMBER ZERO: And also along those lines,

there were some change that happened that all the dentist does is monitor that they have happened, especially with the mandibular advancement, just monitor, yes, the teeth have shifted, but the patient can still chew. The patient does complain about this aesthetically. I guess the men like it having a big, bulging jaw and the women maybe may not like it.

So some of these changes just we can document them, but when do they cross the line of being what we call serious adverse events that impact on health? I don't think we have those definitions right now. At least I don't see them. Maybe Gail can comment on it.

CHAIRPERSON GULYA: Dr. Demko?

DR. DEMKO: Dr. Demko. Basically, I've never had any patient stop wearing an oral appliance that was ragingly effective. So they were willing to put up with massive changes in their bite, in ability to chew, lateral open bites so that they had -- I have a number of patients who are only open on one side in the posterior. These are things that if they are feeling wonderful, they don't care.

And it's pretty much the same with almost any medical treatment, I think the same with CPAP. They're going to wear that, even if they're dating if it makes them feel wonderful the next day. And that is pretty much where the oral appliances are.

CHAIRPERSON GULYA: So we have Dr. Orloff and then Dr. Li. Dr. Orloff?

DR. ORLOFF: Lisa Orloff. I'm not sure where this fits into this discussion. Just thinking about changes that might occur in somebody's mouth that may be perceived as related to the use of the appliance, especially in smokers, I think that patients should be aware that if they have oral mucosal changes, they shouldn't just assume they're related.

One thing you wouldn't want to miss is an evolving cancer in somebody's mouth in the midst of using this kind of device. So somewhere in the labeling or in the -- I'm not sure where that fits, but I don't think we want to overlook complications in the mouth or problems in the mouth that aren't necessarily due to the device but may either be

exacerbated be or falsely attributed to it.

CHAIRPERSON GULYA: Good point. Okay.

Dr. Li?

DR. LI: Kasey Li. I wonder if worsening of sleep apnea qualifies as an adverse event. It certainly is well-described in oral appliance literature, especially in the uncontrolled use of OTC with potentially causing worsening. So I think it is the point of actually looking at the individual data, as opposed to an average or mean improvement of the parameters.

CHAIRPERSON GULYA: Sure. Thank you. Good point.

Any other discussion? Okay. FDA, how are we doing? Sufficient? I see a nod there. We're okay with this one?

(No response.)

CHAIRPERSON GULYA: All right. Now, we have the same questions thrown at us except now we are to say whether or not any of the responses to 3(a) through 3(d) would be different based on the severity of snoring and/or obstructive sleep apnea; i.e., mild,

moderate, or severe.

MEMBER SUZUKI: I'll start.

CHAIRPERSON GULYA: Thank you. Bless you.

MEMBER SUZUKI: Jon Suzuki. My answer is no.

CHAIRPERSON GULYA: Thank you.

I haven't heard from Dr. Terris in a while. I want to make sure he is not falling asleep.

DR. TERRIS: I am listening with interest. I am sort of carefully looking at that question. In terms of the adverse outcomes, I don't think it matters the severity of the disease, whether it is snoring or sleep apnea, but in terms of endpoints, yes. I mean, I guess it makes a big difference.

So from my perspective, if we are looking at efficacy for sleep apnea, it actually doesn't matter what happens to their snoring. It's really just the sleep apnea. So you are looking at two different things. Even though we recognize it is a continuum to reach that threshold for sleep apnea, it just has a different way of looking at it.

So I guess the answer is yes, it does make

a difference, not so much that you --

CHAIRPERSON GULYA: What in specific would you change?

DR. TERRIS: Okay. So (a), sorry, I still don't think we need a control group; (b) the endpoints. Mostly it's the endpoints. So for sleep apnea, it would be improvement of the respiratory disturbance index or the AHI to below five, as Eric suggested. So that is to me the sine qua non. And recognizing Kasey's comments about lowest oxygen saturation, I just think it would be a little bit complicated to acknowledge that.

To me, that would be the endpoint for sleep apnea.

CHAIRPERSON GULYA: And that would be the same regardless of mild, moderate, or severe sleep apnea?

DR. TERRIS: Yes.

CHAIRPERSON GULYA: Okay.

DR. TERRIS: And for snoring, it is so subjective that it really is what the sleep partner has to say about it. Now, you asked a question

earlier about the recordings and decibel loudness. It is interesting because it turns out that for the sleep partner, the volume is not as important as the frequency. That has been carefully shown in a number of different studies using the SNAP as the most common device available out there. That really is for academic purposes more than for reading efficacy of a device.

So I would say the sleep partner is really the one that makes a difference. And so for that reason, for that reason, a control group probably does make sense because that is so subjective and there is no objective way to quantify that data.

CHAIRPERSON GULYA: Okay. All right. Let's see. Who haven't I heard from in a bit here? Dr. Jenkins? You don't have any comments? Okay. Dr. Mair?

DR. MAIR: There was a question about what snoring parameters to measure. What David said is exactly right. There are four snoring parameters, just for the record, that are measured. One is the percentage of snoring originating in the soft palate.

And that can be measured by the frequency.

There is a weighted velum-like or average loudness of the snoring noise. And then there is average loudness of the total snoring noise over the recorded period of time. And then there is average palatal flutter frequency.

I say those things only for the record, not really much to discuss them, but they're easily measured. Those are the four points that have been looked at in multiple studies.

CHAIRPERSON GULYA: And with respect to the severity of the snoring and the obstructive sleep apnea, looking at some of the things we have talked about in terms of what the FDA would want in terms of submissions. How would those change? Depending upon the severity? Use the microphone, please.

DR. MAIR: I think you would look for statistical significance. The palatal flutter frequency, for instance, would increase. And the others would decrease. And then you look for statistical significance and the amount of decrease.

I can't give you a number like a 50

percent or whatever, but all of those, all four of those, one should go up and the other three should go down. That is what has been used in several studies to determine success, objective determination.

CHAIRPERSON GULYA: Is there any information regarding what is thought to be a clinically significant change, reduction in those?

DR. MAIR: As far as in --

CHAIRPERSON GULYA: Well, if you are talking about snoring.

DR. MAIR: Objective we are talking about. I can only say that it would be a statistical significance in the lowering of three and the increase of the palatal flutter frequency. I don't --

CHAIRPERSON GULYA: Anybody have any idea about the clinical change, clinically significant change, in these parameters? Because, again, the statistical significance is going to be kind of at virtue of your numbers and some of your variability.

I am just trying to get a handle on what would be thought -- you know, if I were a patient and this device -- I mean, it always sounds real

impressive to say there is a statistically significant difference in the loudness or frequency of snoring, but it turns out that it is one decibel on a 90 dB sound or whatever.

DR. MAIR: What we see is that -- and several studies look at this, most of the subjective studies, that snoring is absent or snoring is no longer a problem. And those are the two things.

Now, there have also been studies by personal experience is multiple occasions, actually, where someone will come in and say, "I snore very loud." And then we get one of these tests, like, for instance, the SNAP test. And it shows them not snoring. And then we sit down with spouse and say, "This showed not snoring." And then, all of a sudden, this litany of things comes out that actually wasn't snoring being the problem at all, but it was actually other social or marital-type problems.

CHAIRPERSON GULYA: Okay. Any other thoughts on this question number E?

(No response.)

CHAIRPERSON GULYA: All right. Moving on

now to (f). This goes about any specific consideration in trial design for OTC indications. We have kind of all been addressing this as an OTC indication. Yes, Dr. Mann?

DR. MANN: I was wondering if we could just get a little clarification from the panel. It has been brought up a couple of times regarding obstructive sleep apnea that an apnea/hypopnea index of less than five; i.e., returning to a normal physiological level, would be the sine qua non of a complete response.

We heard a couple of people discuss the problems with sleep studies, the variability from night to night, the problems of the first night effect, the home use devices versus the monitored situation.

I was wondering if you could just give a little bit of clarification. You know, I recognize that there are two schools of thought on this but how you would account for the variability and the first night effect and so forth, how many sequential nights or what design would you do in order to get the data

that you needed from either an in-home or a monitored sleep study.

CHAIRPERSON GULYA: Dr. Calhoun?

DR. CALHOUN: In spite of its inherent flaws, the polysomnogram I think remains the gold standard. And I think that to really be convincing, probably two nights in the sleep lab. And if there's not a significant difference, say more than a 10 to 15 percent difference, in the RDI and the minimum O2 saturation between the two nights, then I think it is reasonable to accept that as probably true data. On the other hand, if there is an RDI of 2 on one night and 87 the next night, that may not be sufficient.

CHAIRPERSON GULYA: Dr. Orloff?

DR. ORLOFF: Before we leave the issue of endpoints, I'm not sure we mentioned compliance with the devices. It's something that should be tracked, especially over the long time.

CHAIRPERSON GULYA: Good point. Okay. Compliance with the device. Anything else? Anything further with respect to the variability in the polysomnogram and the home sleep measurements?

Anybody else?

(No response.)

CHAIRPERSON GULYA: Okay. Are you happy with that? Okay. All right. So, anyway, in terms of specific considerations in trial design for OTC indications, I think we have pretty much covered that because that is the way we have been addressing it all along, in terms of OTC considerations. So I think that is kind of a little bit redundant.

All right. So I think we're winding up to the last. Yes, Dr. Runner?

DR. RUNNER: Maybe this is a good time to bring this up. From your initial conversation about oral appliances, you seem to indicate that most people indicated that they were hesitant to have that over-the-counter. However, in the discussion of the endpoints and clinical data, there were some parameters that were discussed about what should be in the study.

If a company were to come to us with a study for OTC use of these intraoral appliances, would that be something we should consider and to what level

and how long should this study be to develop some of the data that you're talking about in terms of the adverse events? Despite the fact that you say you don't think that they necessarily should be OTC, we will be presented with studies to get this indication.

So I wanted just some additional thoughts on that and what kind of study a consumer study would be adequate or not for that indication.

CHAIRPERSON GULYA: Okay. Dr. Terris?

DR. TERRIS: Well, I think that is one of the reasons some of us were reluctant to engage in this discussion, because we didn't want it to be seen as an endorsement of bringing forth these devices for an over-the-counter indication for treatment of sleep apnea.

CHAIRPERSON GULYA: Dr. Runner, if you could speak into the microphone?

DR. RUNNER: Or snoring.

DR. TERRIS: Same comment for snoring.

CHAIRPERSON GULYA: Okay. Got your question answered? I don't think so. No.

MEMBER SUZUKI: Then I'll comment.

CHAIRPERSON GULYA: Okay, Dr. Suzuki.

MEMBER SUZUKI: Jon Suzuki. I agree with Dr. Terris completely that I think our discussions, I hope, don't send a message that these are suitable for OTC discussions or applications. The parameters that I discussed from a dental viewpoint, Dr. Runner, you know as well as I do can only be done by a dentist.

DR. RUNNER: So that when a company comes to us with a consumer-based study where patients are given -- and I have to say the studies that we typically or designs we see is a company comes in and says, "We're going to hand these out in a shopping mall," let's say. And then we have an evaluation sometime later about whether they have decreased snoring, et cetera, and we look at some dental indications.

Those aren't addressing the issues that would be of concern to you in terms of the long-term use or their self-diagnosis. Is that the feeling I am getting from the panel?

CHAIRPERSON GULYA: Yes. And our discussion is a little bit hampered by the fact that